etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc.

The following examples are offered by way of illustration and not by way of limitation.

EXPERIMENTAL

EXAMPLE 1

A.

Background: Therapeutic angiogenesis is a promising option for patients with refractory angina unsuitable for revascularization, but current delivery methods either require open-chest surgery or provide only short-lived, transient exposure to growth factors. This study assessed the feasibility of percutaneous coronary venous cannulation and selective regional injection as a novel approach to local myocardial drug delivery.

Methods and Results: In 13 anesthetized pigs the coronary sinus was cannulated percutaneously and a balloon-tipped catheter was advanced to the anterior interventricular vein (AIV) or middle cardiac vein (MCV). During balloon occlusion, selective venous injection of radiographic contrast (diatrizoate) caused localized myocardial staining. Injection was performed with hyperbaric pressure in 8/13 cases (61%). In the total group, videodensitometric analysis showed that diatrizoate persisted for at least 30 minutes, with 50% clearance over approximately the first 4 minutes (FIG. 1). Venous injection of Evans Blue dye showed that localized, regional infiltration was reproducibly accomplished in targeted myocardial regions: the left ventricular apex, anterior interventricular septum and anterior wall via the AIV and the inferoposterior wall via the MCV.

Conclusions: The percutaneous coronary venous route is a favorable delivery approach for therapeutic angiogenic substances, being reproducibly accessible and facilitating selective regional myocardial delivery and persistence of delivered substances.

B. Intracardiac Venous System as a Novel Conduit for Local Drug Delivery

Background: Effective strategies for administering angiogenic factors involve either multiple myocardial injections or intracoronary delivery into highly diseased conduits. Alternatively, access to cardiac venous system through the coronary sinus provides an extensive network of vessels for regional delivery of angiogenic agents to the distal myocardium.

Methods: Five swine underwent simultaneous right and left heart cardiac catheterization. A 7F balloon tip catheter over a guidewire was used to cannulate the anterior interventricular vein (AIV). 15 μm fluorescent microspheres were used to determine the territory of myocardium that drains into the AIV, and would be potentially available for drug delivery. A different color set of microspheres was used to label the left anterior descending artery territory (through subselective engagement of LAD). All injections were performed over constant time and pressure. Simultaneous ventricular end diastolic pressure (LVEDP), coronary wedge pressure, and distal venous wedge pressure were measured during the balloon inflation. The hearts were harvested and a circumferential sample was divided into eight segments; each segment was divided further into the epicardial and endocardial layers. These samples were processed for microspheres sedimentation, and subjected to scanning fluorometery to determine the amount of different color microspheres in each region. Results: There was no significant increase in the LVEDP, and only transient elevation of VWP during the injections (range of 5 to 30 mm Hg). The concentration of microspheres in the LAD territory was similar in both LAD and AIV injections (93%±3.5 vs. 81%±7.0, respectively). 68% of the microspheres delivered through the AIV localized to the epicardial layer of myocardium vs. 53% delivered through the LAD (endocardial localization after AIV and LAD injections were 32% and 47%, respectively).

Conclusion: These data demonstrate the feasibility of using the cardiac venous system for regional myocardial reagent delivery.

EXAMPLE 2

FIG. 2 provides a representation of administration according to the subject methods in which the vessel walls are disrupted by pressure applied during retrograde administration of the agent, thereby providing for entry of the agent into the interstitial space.

It is evident from the above discussion that the subject invention provides an important new means for locally administering an active agent to a host. Specifically, the subject invention provides a method for locally administering an active agent to an interstitial target site proximal to a vessel. The subject methods are suitable for use in the delivery of a wide variety of different agents, and are particularly suited for use in the delivery of biological agents, such as polypeptides and nucleic acids. One advantage of the subject methods is that they provide a new and convenient methodology for delivering active agents, including biological agents, to the myocardium. Other advantages of the subject methods include the ability to deliver agent to a large region of interstitial space from a single administration point. Additional advantages include the ability of the host to tolerate the mode of administration such that damage caused by the route of administration, if any, is outweighed by the benefits provided by the subject method of administration and the ability to produce inflammation at the site of administration, when desired. As such, the subject invention represents a significant contribution to the art.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

What is claimed is:

1. A method of locally administrating an active agent to a host, said method comprising:

retroinfusing said agent into a vascular vessel of said host under conditions sufficient to produce a disruption in said vessel and for said agent to enter an interstitial space of said host through said disruption so that said agent is locally administered to said host.

2. The method according to claim **1**, wherein said vessel is a vein.

3. The method according to claim **1**, wherein said retroinfusing comprises providing stress to said vascular vessel at a site at least proximal to said interstitial space.

4. The method according to claim 1, wherein said method further comprises using depot means.

5. The method according to claim 1, wherein said method further comprises administration of energy to said vessel.

6. The method according to claim 1, wherein said interstitial space is myocardial interstitial space.

7. The method according to claim 3, wherein said retroinfusing comprises administering said agent at a pressure sufficient to produce at least a mechanical stress on said vessel.

8. A method of locally administering an active agent to a host, said method comprising:

retroinfusing said agent into a vein of said host under conditions sufficient to produce a disruption in said vessel and for said agent to enter an interstitial space of said host through said disruption so that said agent is locally administered to said host.

9. The method according to claim 8, wherein said retroinfusing comprises administering said agent at a pressure sufficient to produce at least a mechanical stress on said vein.

10. The method according to claim 8, wherein said agent is a biological agent selected from the group consisting of peptides, proteins, nucleic acids, lipids, polysaccharides, and mimetics thereof.

11. The method according to claim 8, wherein said method further comprises producing inflamation in said vascular vessel.

12. The method according to claim 8, wherein said interstitial space is myocardial interstitial space.

13. The method according to claim 9, wherein said pressure is sufficient to at least distend said vein.

14. The method according to claim 9, wherein said pressure is sufficient to disrupt said vein.

15. A method of locally administering an active agent to a host, said method comprising:

retroinfusing said agent into a vein of said host with a catheter and at a pressure sufficient to produce a disruption on said vein such that said agent enters an interstitial space proximal to the vein through said disruption;

whereby said agent is locally administered to said host.

16. The method according to claim 15, wherein said pressure is sufficient to at least distend said vein.

17. The method according to claim 16, wherein said pressure is sufficient to disrupt said vein.

18. The method according to claim 16, wherein said agent is a biological agent selected from the group consisting of peptides, proteins, nucleic acids, lipids, polysaccharides, and mimetics thereof.

19. The method according to claim 16, wherein said method further comprises producing inflamation in said vascular vessel.

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